# Exhibit 48

*Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments* (April 2021)

# Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments

*Technical Specifications Document*

**Associated Guidance Documents and Conformance Guide:**

**Draft Guidance for Industry: Providing Submissions in Electronic Format – Postmarketing Safety Reports (June 2014)**

**Guidance for Industry and FDA Staff: Postmarketing Safety Reporting for Combination Products (July 2019)**

**Draft Guidance for Industry: Providing Regulatory Submissions in Electronic Format: IND Safety Reports (October 2019)**

**Electronic Submissions of IND Safety Reports Technical Conformance Guide (October 2019)**

For questions regarding this technical specifications document, contact the Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, Food and Drug Administration, at FAERSESUB@fda.hhs.gov; or Office of Communication, Outreach and Development, Center for Biologics Evaluation and Research, Food and Drug Administration, at CBERICSRSubmissions@fda.hhs.gov.

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**
**Center for Biologics Evaluation and Research (CBER)**

**April 2021**

# Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments

## Revision History Table

| Date | Version | Summary of Changes |
|---|---|---|
| 2008-06-11 | 1.0 | Initial Version |
| 2008-08-06 | 1.1 | Added Filename format information |
| 2008-10-10 | 1.2 | Updated UTF-8 to ISO-8859-1 encoding; indicated simultaneous acceptance of ICSR and ICSR attachments; provided another acceptable file extension for SGML files; and clarified use of abbreviations (NDA, ANDA, and STN) |
| 2008-10-22 | 1.3 | Provided clarification in Section II; updated footnote 3; and added new paragraph to Section V.C. |
| 2013-07-05 | 1.4 | Updated AERS to FAERS migration changes, removed references to SGML file formatting, incorporated updates from CBER |
| 2018-02-06 | 1.5 | Added a new section to highlight data fields for reporting ICSRs on Combination Products |
| 2019-09-30 | 1.6 | Added two new sections to provide regional data elements for electronic submissions of certain IND safety reports (section I) and IND-exempt Bioavailability (BA)/Bioequivalence (BE) studies (section J).<br><br>Added an appendix (II) highlighting various case scenarios for electronic submissions of IND safety reports to FAERS. |

| | | |
|---|---|---|
| 2020-02-11 | 1.7 | Added a new value to the data element B.4.k.1 for drug characterization to accommodate a similar device.<br><br>Updated the data element B.4.k.18.2 to specify values.<br><br>Updated the data element B.4.k.18.3 to use default value. |
| 2020-12-18 | 1.8 | Added a new regional data element A.1.FDA.16 (FDA Safety Report Type) in Table 2 Detailed Description of Administrative Tags<br><br>Added section Submission Rules<br><br>Added a new value to the data element B.4.k.1 and B.4.k.19 in section J. IND-exempt BA/BE Studies |
| 2021-03-26 | 1.9 | Updated section XML Header to include DTD 3.0 for premarketing reporting<br><br>Updated the reference description to data element A.1.FDA.16 in Table 2 Detailed Description of Administrative Tags<br><br>Updated section ICSR Message Header Information to include information in premarketing reporting<br><br>Updated section AS2 Headers and Routing IDs for Premarketing Safety Report Submissions<br><br>Updated section Submission Rules |

# *Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments*

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# Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments

This document provides current specifications for submitting individual case safety reports (ICSRs) and ICSR attachments in electronic form. The specifications apply to electronic submission of ICSRs for drug and biological products studied under an investigational new drug application (IND) (including bioequivalence studies conducted under IND), ICSRs from IND-exempt bioavailability (BA)/bioequivalence (BE) studies, and ICSRs for marketed drug and biological products and combination products to the FDA Adverse Event Reporting System (FAERS). The specifications do not apply to the following marketed biological products: prophylactic vaccines, whole blood or components of whole blood, human cells, tissues, and cellular and tissue-based products (HCT/Ps) regulated by FDA.

This document discusses the technical specifications for electronic submission of ICSRs and ICSR attachments through the FDA Electronic Submissions Gateway (ESG).[1] ICSRs (and any ICSR attachments) are to be prepared in accordance with the International Council for Harmonisation (ICH) E2B(R2) data elements in extensible markup language (XML) file format for compatibility with the FAERS database. ICSRs for marketed products should not be submitted to the electronic Common Technical Document (eCTD).[2]

If you have not previously submitted an ICSR in electronic format to FAERS, you should contact the FAERS electronic submission coordinator at faersesub@fda.hhs.gov and they will assist you with submission of a test file.

## I. ELECTRONIC SUBMISSIONS OF ICSRS AND ICSR ATTACHMENTS

Each initial ICSR or follow-up ICSR may consist of structured information and non-structured information, such as ICSR attachments.

For the FDA to process, review, and archive the ICSRs, prepare your ICSRs for electronic submission by following these steps:

- Provide a unique filename for the submission; see section II of this document.
- Add a file header and file extension; see section IV of this document.
- Populate the elements of the ICSR file; see section V of this document.

[1] For information on providing submissions using the ESG, refer to https://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm.

[2] See FAERS Electronic Submissions at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115894.htm.

- If applicable, add ICSR attachments to ICSRs; see section VI of this document.

## II. SUBMISSION FILE NAME

Each electronic submission of ICSRs or attachments to ICSRs must have a unique filename (e.g., your named file + date and time stamp down to the second: filenameYYYYMMDDHHMMSS). You may choose your own format to maintain uniqueness.

## III. ICSR ACKNOWLEDGEMENTS

### A. ESG Acknowledgement

After submitting an ICSR or ICSR attachment, you should receive an ESG message delivery notice (MDN) notifying the sender of the receipt of their submission, but not acknowledging the acceptance of the submission. If the MDN is not received within 2 hours, go to the ESG System Status web page. If the ESG web page is non-operational, go to the ESG Home Page for further information.

### B. FAERS Acknowledgment

The MDN is then followed by a FAERS acknowledgment within 2 hours of the ESG acknowledgement. The FAERS acknowledgement notifies the sender whether their submission has been processed. If you do not receive the FAERS acknowledgement, resubmit the ICSRs without changing the filename.

If you receive a report acknowledgement code 02, indicating that your submission did not process due to file error/s that are specified in the acknowledgment, then proceed as follows:

- For submission with a single ICSR, resubmit the corrected ICSR with a new unique filename.

- For a submission consisting of multiple ICSRs, if one or more ICSRs in the submission failed to process, separate those ICSRs from the processed ICSRs, correct them and resubmit only the corrected ICSRs as a new submission with a unique filename. For example, if there were 50 ICSRs in an original submission and 15 of them failed to process, then only those 15 ICSRs must be separated, corrected appropriately, and resubmitted with a new unique filename. The resubmission should not contain any of the previously processed ICSRs.

## IV. ELECTRONIC TRANSPORT FORMAT: XML FILES

FDA accepts the data elements defined in the "Guidance for Industry E2BM Data Elements for

Transmission of Individual Case Safety Reports (April 2002)."[3] The ICH E2B(R2) guidance provides additional information and clarification of the previously issued guidances.[4]

The electronic transport format also known as the Document Type Definition (DTD) for XML files is described in the associated document "XML Formatted DTD" (DTD Version 2.1, DTD Version 2.2 and DTD Version 3.0) (see links to the documents below in section C).

### A. AS2 Headers and Routing IDs for Postmarketing Safety Report Submissions

For postmarketing safety report submissions, the sponsors should include the unique AS2 headers or routing IDs for safety reports and attachments in one of the two ways listed below.

- AS2 Headers
  - Destination: "CDER"
  - XML files: AERS
  - PDF's: AERS_ATTACHMENTS

or

- Routing IDs
  - XML files: FDA_AERS
  - PDF's: FDA_AERS_ATTACHMENTS

### B. AS2 Headers and Routing IDs for Premarketing[5] Safety Report Submissions

For premarketing safety report submissions, the sponsors should include the unique AS2 headers or routing IDs for premarketing safety reports and attachments, as listed below, to differentiate these reports between CDER and CBER, and from postmarketing ICSRs.

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[3] For information on Guidance for Industry on E2BM Data Elements for Transmission of Individual Case Safety Reports, please refer to the following:

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073092.pdf.

[4] See the guidance for industry entitled *E2B Data Elements for Transmission of Individual Case Safety Reports* (January 1998) (E2B). FDA currently supports use of E2B data elements in addition to the E2BM data elements. However, it is preferred that ICSRs be submitted with E2BM data elements to allow for the most efficient processing of the submissions. For those who wish to use E2B data elements and the corresponding electronic transport format (ICH M2 Electronic Transmission of Individual Case Safety Reports Message Specification Final Version 2.3 Document Revision February 1, 2001 (ICH ICSR DTD Version 2.1)), please refer to documentation provided at https://www.fda.gov/downloads/drugs/ucm149932.pdf

[5] The term premarketing safety report refers to IND safety reports and IND-exempt BA/BE studies safety reports.

***1. Submitting premarketing safety reports for CDER IND and IND-Exempt BA/BE***

- AS2 Headers
  - Destination: "CDER"
  - XML files: AERS_PREMKT_CDER
  - PDF's: AERS_ATTACHMENTS_PREMKT_CDER

or

- Routing IDs
  - XML files: FDA_AERS_PREMKT_CDER
  - PDF's: FDA_AERS_ATTACHMENTS_PREMKT_CDER

***2. Submitting premarketing safety reports for CBER IND***

- AS2 Headers
  - Destination: "CBER"
  - XML files: AERS_PREMKT_CBER
  - PDF's: AERS_ATTACHMENTS_PREMKT_CBER

or

- Routing IDs
  - XML files: FDA_AERS_PREMKT_CBER
  - PDF's: FDA_AERS_ATTACHMENTS_PREMKT_CBER

### C. XML Header

The addition of an XML header enables FDA to process ICSRs in an XML format successfully. FDA supports only the ISO-8859-1 character set for encoding the submissions.

***1. For submissions of postmarketing safety reports for drug and biological products, add the following XML header to the ICSR file:***

<?xml version="1.0" encoding="ISO-8859-1"?>

<!DOCTYPE ichicsr SYSTEM "https://www.accessdata.fda.gov/xml/icsr-xml-v2.1.dtd">

***2. For submissions of postmarketing safety reports for combination products, add the following XML header to the ICSR file:***

<?xml version="1.0" encoding="ISO-8859-1"?>

<!DOCTYPE ichicsr SYSTEM "https://www.accessdata.fda.gov/xml/icsr-xml-

v2.2.dtd">

***3. For submissions of premarketing safety reports, add the following XML header to the ICSR file:***

<?xml version="1.0" encoding="ISO-8859-1"?>

<!DOCTYPE ichicsr SYSTEM "https://www.accessdata.fda.gov/xml/icsr-xml-v3.0.dtd">

### D. ICSR Message Header Information

***1. For submissions of postmarketing drug and biological product safety reports, use the value "2.1" for the DTD Descriptor <messageformatversion>:***

<messageformatversion>2.1</messageformatversion>

***2. For submissions of postmarketing combination product safety reports, use the value "2.2" for the DTD Descriptor <messageformatversion>:***

<messageformatversion>2.2</messageformatversion>

***3. For submissions of premarketing safety reports, use the value "3.0" for the DTD Descriptor <messageformatversion>:***

<messageformatversion>3.0</messageformatversion>

### E. ICSR File Extension

Use "xml" as the file extension for ICSRs in XML format. The name of the file should be 200 characters or less, excluding the three-digit extension. FDA does not support file names with multiple periods "." or the use of any special or foreign characters except underscore "_" and dash "-".

## V. DATA ELEMENTS FOR ELECTRONIC SUBMISSIONS

### A. Minimum Data Elements Requirements

For a submission to be successfully processed, submit an ICSR with the minimum data elements for reporting that are appropriate for the product type. If a sponsor submits an ICSR without the minimum data elements, they will receive a FAERS acknowledgement code 02 stating that the submission was not processed (see section III.B above). The minimum data elements for reporting are provided in Table 1 and the bullets that follow list the data elements to include in an ICSR by product type.

**Table 1. Minimum Data Elements**

| Element | Data |
|---|---|
| B.1 | Identifiable Patient |
| A.2 | Identifiable Reporter |
| B.2 | Reaction or Event |
| B.4 | Suspect Drug Product |

- Adverse event reports submitted for unapproved prescription drug products, unapproved nonprescription drug products and products approved for marketing under an abbreviated new drug application (ANDA), biologics license application (BLA), or new drug application (NDA), including combination products should have, at a minimum, the four data elements listed in Table 1.

- Adverse event reports for compounded drugs submitted by registered outsourcing facilities should have at a minimum, a suspect product and an adverse event.

- IND safety reports should include, at a minimum, the four data elements listed in Table 1 and the IND number under which the clinical trial where the event occurred is conducted.

- Serious adverse event reports from IND-exempt BA/BE studies should include, at a minimum, the four data elements listed in Table 1 and the pre-assigned ANDA number (hereafter referred as, Pre-ANDA number).

### B. Administrative and Identification Elements

For FDA to successfully process your electronic ICSR submissions, populate the administrative and identification elements as indicated in Table 2.

**Table 2. Detailed Description of Administrative Tags***

| Element | DTD Descriptor 2.1 | Length | Element Values for DTD 2.1 |
|---|---|---|---|
| A.1.9 | <fulfillexpeditecriteria> | 1N | 1= Yes (15-Day expedited)<br>2= No (non-expedited)<br>4= 5-Day<br>5= 30-Day<br>6= 7-Day expedited |
| A.1.0.1 | <safetyreportid> | 100AN | Sender's (Case) Safety Report Unique Identifier† |
| A.1.10.1 | <authoritynumb> | 100AN | Regulatory authority's case report number |
| A.1.10.2 | <companynumb> | 100AN | Other sender's case report number |
| A.3.1.2 | <senderorganization> | 60AN | Sender identifier |
| A.2.3.2^ | <sponsorstudynumb> | 35AN | IND or Pre-ANDA number under which the clinical trial where the event occurred is conducted |
| A.1.FDA.16†† | <fdasafetyreporttype> | 1N | 1=IND Safety Report<br>2=IND-Exempt BA/BE Safety Report<br>3=Postmarketing Safety Report |

* Include either <companynumb> or <authoritynumb> values. FDA cannot process the ICSR without one of these element values.

† The Sender's Safety Report Unique Identifier is comparable to the Manufacturer Report Number (also referred to as the Manufacturer Control Number (MCN)) provided on paper in FDA Form 3500A. This number is the company's unique case identification number, which is used for the life of the case.

^ For IND and IND-exempt BA/BE study safety reports only. An IND-exempt BA/BE study refers to a BA/BE study not conducted under IND.

†† The FDA Safety Report Type data element distinguishes premarketing (IND and IND-Exempt BA/BE) safety reports from postmarketing safety reports and is used to determine which reports are posted publicly. The FDA Safety Report Type data element is optional when using DTD 2.1 and 2.2 for postmarketing safety report submission but is mandatory when using DTD 3.0 for premarketing safety report submission.

### C. Authorization/ Application Number Format

In the section designated for drug and biological products information, use the following format for the "Authorization/ Application Number" element (B.4.k.4.1) <drugauthorizationnumb> as indicated in Table 3 and described below.

- For approved drug and biological products marketed under an approved application, include the acronym "NDA" or "ANDA," followed by a space and then the number for the application (e.g., NDA 012345, ANDA 012345). For prescription drug products marketed without an approved application (Rx No Application), use "000000." For a nonprescription drug product marketed without an approved application (Non-Rx No

Application), use "999999." For adverse event reports for compounded drug products submitted by registered outsourcing facilities, use "COMP99."

- For marketed biological products, include the appropriate acronym "BLA," "STN," or "PLA" followed by a space and the primary six-digit number (e.g., STN 123456).

**Table 3. Detailed Description of Application Number Formats**

| Type of Application | Recommended Format |
|---|---|
| NDA/ ANDA | NDA, ANDA 012345 |
| STN/ BLA/ PLA | STN or BLA or PLA 123456 |
| Rx No Application | 000000 |
| Non-Rx No Application | 999999 |
| Compounded Products | COMP99 |

### D. Unique Case Identification Numbers for Initial and Follow-Up ICSRs

For the follow-up ICSR safety reports to be correctly linked to your initial ICSR report, follow these steps:

- Use the same <safetyreportid> for the E2BM elements in section A.1.0.1 for the initial ICSR and any of its follow-up ICSRs; this allows the follow-up report to be linked to the initial report in the FAERS database.

- If the initial ICSR was submitted on paper but its follow-up ICSR is submitted electronically, include the Manufacturer Control Number (MCN) listed in Box G9 of the FDA paper Form 3500A from the initial report in both A.1.0.1 <safetyreportid> and in A.1.10.2 <companynumb> field in the follow-up electronic submission.

- Always use the <safetyreportid> that was assigned to the initial ICSR when submitting follow-up reports. If you need to change the <safetyreportid> internally, note the internally reassigned <safetyreportid> in the narrative section of the follow-up report (i.e., element B.5.1) (e.g., "This ICSR has been reassigned to the Company ID number COA12345"). Do not use the internally reassigned <safetyreportid> for any follow-up reports.

- In the event that an incorrect <safetyreportid> has been used in a follow-up report, contact the FAERS electronic submission coordinator at faersesub@fda.hhs.gov so that the follow-up ICSR can be matched to the initial ICSR.

### E. MedDRA Specific Elements

Use the ICH Medical Dictionary for Regulatory Activities (MedDRA) to code medical

terminology.[6] When possible, use the Lowest Level Term (LLT), and record the LLT as the MedDRA numeric code rather than the LLT name (e.g., the LLT name is Rash; the MedDRA numeric code for LLT Rash is 10378444).

### *1. Reaction/Event*

#### a) Reaction/Event as reported by the primary source field

Record the original reporter's words verbatim and/or use short phrases to describe the reaction/event in element (B.2.i.0).

#### b) Reaction/Event MedDRA Term LLT numeric code or text field

Record the MedDRA LLT that most closely corresponds to the term reported by the original reporter in element (B.2.i.1).

#### c) Reaction/Event MedDRA Preferred Term (PT) numeric code or text field

Record the MedDRA PT that most closely corresponds to the term reported by the original reporter in element (B.2.i.2).

### *2. Other E2B Elements*

For the E2B elements listed in Table 4, use either MedDRA text or, preferably, the corresponding numeric code.

**Table 4. Additional E2B Elements for Preferred MedDRA Coding**

| Element | DTD Descriptor 2.1 | Length |
|---|---|---|
| B.1.7.1a.2 | <patientepisodename> | 250 AN |
| B.1.8f.2 | <patientdrugindication> | 250 AN |
| B.1.8g.2 | <patientdrugreaction> | 250 AN |
| B.1.9.2b | <patientdeathreport> | 250 AN |
| B.1.9.4b | <patientdetermineautopsy> | 250 AN |
| B.1.10.7.1a.2 | <parentmedicalepisodename> | 250 AN |
| B.1.10.8f.2 | <parentdrugindication> | 250 AN |
| B.1.10.8g.2 | <parentdrugreaction> | 250 AN |
| B.3.1c | <testname> | 100 AN |
| B.4.k.11b | <drugindication> | 250 AN |
| B.4.k.17.2b | <drugrecuraction> | 250 AN |
| B.4.k.18.1b | <drugreactionasses> | 250 AN |
| B.5.3b | <senderdiagnosis> | 250 AN |

[6] Companies can license MedDRA from an international maintenance and support services organization (MSSO) (toll free number 877-258-8280; Direct 571-313-2574; fax 571-313-2345; e-mail MSSOhelp@mssotools.com).

### F. Drug Description and Case Narrative Elements

To ensure the successful processing of your electronic ICSR submission, applicants are advised to populate the drug description and narrative elements as indicated in Table 5.

**Table 5. Detailed Description of Drug(s) and Narrative Elements*†**

| Element | DTD Descriptor 2.1 | Length | Element Values for DTD 2.1 |
|---|---|---|---|
| B.4.k.1 | <drugcharacterization> | 1N | 1=Suspect<br>2=Concomitant<br>3=Interacting<br>4=Drug not administered |
| B.4.k.2.1 | <medicinalproduct> | 70AN | Proprietary Medicinal Product Name |
| B.4.k.2.2 | <activesubstancename> | 100AN | Drug Substance Name |
| B.5.1 | <narrativeincludeclinical> | 20000AN | Case Narrative |

*Include <medicinalproduct> and/or <activesubstancename>. FDA cannot process the ICSR without at least one of these elements.
†Appendix I lists various examples of correct drug element formats.

#### *1. Recording Multiple Drugs*

If you are submitting safety reports for products containing multiple drugs, you should follow these steps:

- List the proprietary drug product name in element (B.4.k.2.1) and/or list the drug substance name in element (B.4.k.2.2).
- List the characterization of each reported drug's role, such as suspect, concomitant, interacting, drug not administered, or similar device in element (B.4.k.1).

#### *2. Medicinal Product Name and Active Drug Substance Name*

FDA validates medicinal product names to the available Structured Product Labeling (SPL)[7], the submitted label (as ICSR attachment), and the Substance Registration System (SRS). These are further described below:

- When the product has an SPL, use the same naming convention as it appears in the SPL when submitting the ICSR.

[7] The SPL is a document markup standard approved by Health Level Seven (HL7) and adopted by FDA as a mechanism for exchanging product and facility information. See https://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

- When submitting a product label as an attachment to an ICSR, use the name as it appears on the submitted product label.
- If no medicinal product is named and only the active substance is named, use the name of the active substance as it appears in the SRS.[8]

#### *3. Case Narrative*

##### a) Initial ICSR

Record all case narrative information including clinical course, therapeutic measures, outcome, and all additional relevant information in element (B.5.1). If the information exceeds the field length, consider describing the information using fewer words. Although the use of only the most widely used medical abbreviations is permissible if necessary, their use should be limited when possible.

##### b) Follow-up ICSR

Record both new information and corrections to previously submitted ICSRs in element (B.5.1).

## G. Other Data Elements

#### *1. Dosage Information Field*

If dosage information cannot be captured in the structured fields in B.4.k.5, then use the element (B.4.k.6) <drugdosagetext>.

#### *2. Pharmaceutical Form Field*

Record the pharmaceutical form in element (B.4.k.7) <drugdosageform>. FDA accepts the European Medicines Agency (EMA) dosage codes or text.[9]

#### *3. Route of Administration Field*

Code the route of administration in element (B.4.k.8) <drugadministrationroute> as described in the ICH E2B(R2) guidance.

#### *4. Receiver Field (A.3.2)*

Complete the receiver using the code or text listed in Table 6.

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[8] https://www.fda.gov/ForIndustry/DataStandards/SubstanceRegistrationSystem-UniqueIngredientIdentifierUNII/default.htm.

[9] For a complete list of EMA dosage form codes and text, please refer to https://www.ema.europa.eu/documents/other/list-pharmaceutical-dosage-forms_en.xls

**Table 6. Receiver Information**

| Element | DTD Descriptor 2.1 | Code or Text |
|---|---|---|
| A.3.2.1 | <receivertype> | 2 |
| A.3.2.2a | <receiverorganization> | FDA |
| A.3.2.2b | <receiverdepartment> | Office of Surveillance and Epidemiology |
| A.3.2.2d | <receivergivename> | FAERS |
| A.3.2.3a | <receiverstreetaddress> | 10903 New Hampshire Avenue |
| A.3.2.3b | <receivercity> | Silver Spring |
| A.3.2.3c | <receiverstate> | MD |
| A.3.2.3d | <receiverpostcode> | 20993 |
| A.3.2.3e | <receivercountrycode> | US |
| A.3.2.3l | <receiveremailaddress> | faersesub@fda.hhs.gov |

#### *5. Message Receiver Field (M.1.6)*

The following two message receiver identifiers are used by FDA to distinguish between test and production submissions:

- Test ICSRs: <messagereceiveridentifier>ZZFDATST</messagereceiveridentifier>
- Production ICSRs: <messagereceiveridentifier>ZZFDA</messagereceiveridentifier>

### H. Data Elements for Electronic Submissions of Safety Reports for Postmarketing Combination Products

To ensure the successful processing of your electronic ICSR submission for a marketed drug- or therapeutic biologic led- combination product (e.g., a combination product containing a drug/biologic and device and marketed under an NDA or a BLA), you should populate the data elements indicated in Table 7.

Note: Some of the DTD descriptors listed in Table 7 are under existing E2B(R2) header elements, and some DTD descriptors are under new data elements. Those data element numbers that are new, have the word "FDA" incorporated into the number and are U.S.-specific regional elements related to reporting on combination products.

**Table 7. Combination Product Data Elements**

| Data Element | DTD Descriptor 2.2 | Title | Description | Length | Element Values for DTD 2.2 | Notes |
|---|---|---|---|---|---|---|
| M.1.2 | <messageformatversion> | Message Format Version | Version number of Message Format | 3AN | 2.2 | Use value 2.2 if using icsr-xml-v2.2.dtd<br><br>Use value 2.1 if using icsr-xml-v2.1.dtd |
| A.1 | <safetyreport> | Header/ Entity | Identification of the case safety report | | | |
| A.1.9 | <fulfillexpeditecriteria> | Does this case fulfill the local criteria for an expedited report | | 1N | 1=Yes<br>2=No<br>4=5-Day<br>5=30-Day | Element values= 1 for 15-Day Expedited* and 2 for periodic non-expedited†<br><br>Element value= 4 for remedial action to prevent an unreasonable risk of substantial harm to the public health<br><br>Element value= 5 for malfunction with no associated adverse event<br><br>Do not use element value of 3. |
| A.1.FDA.15 | <combinationproductreport> | Combination Product Report Flag | Combination Product Report Flag | 1N | 1=Yes<br>2=No | |
| A.2 | <primarysource> | Primary source(s) of information | Header/ Entity | | Area below should be a repeatable block | |

| Data Element | DTD Descriptor 2.2 | Title | Description | Length | Element Values for DTD 2.2 | Notes |
|---|---|---|---|---|---|---|
| A.2.1 | | Primary source(s) | Header | | | |
| A.2.1.3.FDA.4 | <reporteremailaddress> | Reporter's Email Address | | 100AN | | |
| B.1.1 | <patientinitial> | Patient | Patient Identifier | 10AN | | If a single report is reported for a malfunction with no adverse event, the element value should be "NONE."<br><br>If there are multiple malfunction reports with no adverse event, then the element value should be "SUMMARY." |
| B.4 | <drug> | Drug(s) Information | Header/ Entity | | Area below should be a repeatable block | |
| B.4.k.1 | <drugcharacterization> | Characterization of drug role | | 1N | 1=Suspect<br>2=Concomitant<br>3=Interacting<br>5=Similar Device | If the product in the report is about a similar device, the element value should be 5=Similar Device. |
| B.4.k.2 | | Drug Identification | Header | | | |
| B.4.k.2.4.FDA.1a | <expirationdateformat> | Expiration date format | Product Expiration date | 3N | 102=CCYYMMDD<br>610=CCYYMM<br>602=CCYY | |
| B.4.k.2.4.FDA.1b | <expirationdate> | Expiration date | Product Expiration date | 8N | | |

| Data Element | DTD Descriptor 2.2 | Title | Description | Length | Element Values for DTD 2.2 | Notes |
|---|---|---|---|---|---|---|
| B.4.k.2.FDA.5 | <productavailableforevaluation> | Product available for evaluation | Indicate whether product is available for evaluation | 1N | 1=Yes<br>2=No<br>3=Return | |
| B.4.k.2.6.FDA.1a | <productreturndateformat> | Product return date format | Date Format | 3N | 102=CCYYMMDD<br>610=CCYYMM<br>602=CCYY | |
| B.4.k.2.6.FDA.1b | <productreturndate> | Product return date | Date when Product was returned | 8N | | |
| B.4.k.20.FDA.1 | <brandname> | Brand Name | The trade or proprietary name of the device constituent part of the suspect combination product as used in product labeling or in the catalog | 80AN | | At least one of the 3 must be reported <brandname> or <commondevicename> or <productcode> for the device constituent part |
| B.4.k.20.FDA.2 | <commondevicename> | Common Device Name | Generic or common name of the device constituent part of the suspect combination product or a generally descriptive name | 80AN | | At least one of the 3 must be reported <brandname> or <commondevicename> or <productcode> for device constituent part |
| B.4.k.20.FDA.3 | <productcode> | Product Code | Product code | 3AN | http://www.acce | At least one of the 3 must be |

| Data Element | DTD Descriptor 2.2 | Title | Description | Length | Element Values for DTD 2.2 | Notes |
|---|---|---|---|---|---|---|
| | | | assigned to the device constituent part based upon the medical device product classification | | ssdata.fda.gov/premarket/ftparea/foiclass.zip | reported <brandname> or <commondevicename> or <productcode> for device constituent part |
| B.4.k.20.FDA.4 | <manufacturer> | Manufacturer | Header/ Entity | | | |
| B.4.k.20.FDA.4a | <manufacturername> | Device Manufacturer Name | Manufacturer name of the device constituent part of the suspect combination product | 100AN | | |
| B.4.k.20.FDA.4b | <manufactureraddress> | Manufacturer Address | Manufacturer address of the device constituent part of the suspect combination product | 100AN | | |
| B.4.k.20.FDA.4c | <manufacturercity> | Manufacturer City | Manufacturer city of the device constituent part of the suspect combination product | 35AN | | |
| B.4.k.20.FDA.4d | <manufacturerstate> | Manufacturer State | Manufacturer state of the device | 40AN | | |

| Data Element | DTD Descriptor 2.2 | Title | Description | Length | Element Values for DTD 2.2 | Notes |
|---|---|---|---|---|---|---|
| | | | constituent part of the suspect combination product | | | |
| B.4.k.20.FDA.4e | <manufacturercountry> | Manufacturer Country | Manufacturer country of the device constituent part of the suspect combination product | 2AN | ISO3166 | |
| B.4.k.20.FDA.5 | <modelnumber> | Model Number | Model number of the device constituent part | 30AN | | |
| B.4.k.20.FDA.6 | <catalognumber> | Catalog Number | Catalog number of the device constituent part | 30AN | | |
| B.4.k.20.FDA.7 | <serialnumber> | Serial Number | Serial number of the device constituent part | 30AN | | |
| B.4.k.20.FDA.8 | <udinumber> | Unique Identifier UDI# | Unique identifier of the device constituent part | 50AN | | |
| B.4.k.20.FDA.9a | <dateimplantedformat> | Device Implant Date Format | Date format of device implant in the patient | 3N | 102=CCYYMMDD<br>610=CCYYMM<br>602=CCYY | For medical devices that are implanted in the patient, provide the implant date or best estimate. If day is unknown, month and year are acceptable. If month and day are unknown, year is acceptable |

| Data Element | DTD Descriptor 2.2 | Title | Description | Length | Element Values for DTD 2.2 | Notes |
|---|---|---|---|---|---|---|
| B.4.k.20.FDA.9b | <dateimplanted> | Device Implant Date | Date of device implant in the patient | 8N | | For medical devices that are implanted in the patient, provide the implant date or best estimate. If day is unknown, month and year are acceptable. If month and day are unknown, year is acceptable |
| B.4.k.20.FDA.10a | <dateexplantedformat> | Device Explant Date Format | Date format of device explant from the patient | 3N | 102=CCYYMMDD<br>610=CCYYMM<br>602=CCYY | If an implanted device was removed from the patient, provide the explant date or best estimate. If day is unknown, month and year are acceptable. If month and day are unknown, year is acceptable |
| B.4.k.20.FDA.10b | <dateexplanted> | Device Explant Date | Date of device explant from the patient | 8N | | If an implanted device was removed from the patient, provide the explant date or best estimate. If day is unknown, month and year are acceptable. If month and day are unknown, year is acceptable |
| B.4.k.20.FDA.11a | <deviceage> | Approximate age of device/ product | Age of device constituent part | 5N | | |
| B.4.k.20.FDA.11b | <deviceageunit> | Approximate age unit of device/ | Age unit of device constituent part | 3N | 800=Decade<br>801=Year<br>802=Month | |

| Data Element | DTD Descriptor 2.2 | Title | Description | Length | Element Values for DTD 2.2 | Notes |
|---|---|---|---|---|---|---|
| | | product | | | 803=Week<br>804=Day<br>805=Hour | |
| B.4.k.20.FDA.12 | <labeledsingleusedevice> | Single Use Device | Indicate whether the device constituent part was labeled for single use or not | 1N | 1=Yes<br>2=No | |
| B.4.k.20.FDA.13a | <devicemanufacturedateformat> | Device Manufacture Date Format | Device Manufacture Date format | 3N | 102=CCYYMMDD<br>610=CCYYMM<br>602=CCYY | |
| B.4.k.20.FDA.13b | <devicemanufacturedate> | Device Manufacture Date | Device Manufacture Date | 8N | | |
| B.4.k.20.FDA.14 | | Remedial action initiated/ Remedial action taken for the product | Header | | | |
| B.4.k.20.FDA.14.1a | <remedialactionrecall> | Recall | Recall initiated | 1N | 1=Yes<br>2=No | |
| B.4.k.20.FDA.14.1b | <remedialactionrepair> | Repair | Repair initiated | 1N | 1=Yes<br>2=No | |
| B.4.k.20.FDA.14.1c | <remedialactionreplace> | Replace | Replace initiated | 1N | 1=Yes<br>2=No | |
| B.4.k.20.FDA.14.1d | <remedialactionrelabel> | Relabeling | Relabeling initiated | 1N | 1=Yes<br>2=No | |
| B.4.k.20.FDA.14.1 | <remedialactionnotify> | Notification | Notification | 1N | 1=Yes | |

| Data Element | DTD Descriptor 2.2 | Title | Description | Length | Element Values for DTD 2.2 | Notes |
|---|---|---|---|---|---|---|
| e | | | initiated | | 2=No | |
| B.4.k.20.FDA.14.1f | <remedialactioninspection> | Inspection | Inspection initiated | 1N | 1=Yes<br>2=No | |
| B.4.k.20.FDA.14.1g | <remedialactionpatientmonitor> | Patient monitoring | Patient monitoring | 1N | 1=Yes<br>2=No | |
| B.4.k.20.FDA.14.1h | <remedialactionmodifyadjust> | Modification/ Adjustment | Modification/ Adjustment initiated | 1N | 1=Yes<br>2=No | |
| B.4.k.20.FDA.14.1i | <remedialactionother> | Other | Other Remedial Action initiated | 75AN | | |
| B.4.k.20.FDA.15 | <deviceusage> | Device Usage | Indicate the use of the device constituent part of the suspect combination product | 1N | 1=Initial Use of Device<br>2=Reuse<br>3=Unknown | |
| B.4.k.20.FDA.16 | <devicelotnumber> | Device Lot Number | Lot number of the device constituent part of the suspect combination product | 35AN | | |
| B.4.k.20.FDA.17 | <malfunction> | Malfunction | Malfunction of product | 1N | 1=Yes<br>2=No | |
| B.4.k.20.FDA.18 | | Follow-up type | Header | | | |
| B.4.k.20.FDA.18.1a | <followupcorrection> | Correction | Correction | 1N | 1=Yes<br>2=No | |
| B.4.k.20.FDA.18.1b | <followupadditionalinfo> | Additional information | Additional information | 1N | 1=Yes<br>2=No | |
| B.4.k.20.FDA.18.1 | <followupresponsetoFDA> | Response to | Response to FDA | 1N | 1=Yes | |

| Data Element | DTD Descriptor 2.2 | Title | Description | Length | Element Values for DTD 2.2 | Notes |
|---|---|---|---|---|---|---|
| c | | FDA request | request | | 2=No | |
| B.4.k.20.FDA.18.1d | <followupdeviceevaluation> | Device Evaluation | Device Evaluation | 1N | 1=Yes<br>2=No | |
| B.4.k.20.FDA.19 | <deviceproblemandevaluation> | Device Problem and evaluation codes | Header/ Entity | | Area Below Should be a Repeatable Block | |
| B.4.k.20.FDA.19.1a | <evaluationtype> | Evaluation Type | Type of problem and/or the evaluation | 2N | 01=Device Problem<br>02=Method<br>03=Result<br>04=Conclusion | |
| B.4.k.20.FDA.19.1b | <evaluationvalue> | Evaluation Value | The FDA code value based on the respective evaluation type | 6N | | The value depends on the respective <evaluationtype><br><br>If <evaluationtype> = 01 --> https://www.fda.gov/media/146825/download<br><br>If <evaluationtype> = 02 --> https://www.fda.gov/media/146827/download<br><br>If <evaluationtype> = 03 --> https://www.fda.gov/media/146828/download<br><br>If <evaluationtype> = 04 --> https://www.fda.gov/media/146829/download |
| B.4.k.20.FDA.20 | <operatorofdevice> | Operator of | Operator of the | 100AN | | Use the value “Health |

| Data Element | DTD Descriptor 2.2 | Title | Description | Length | Element Values for DTD 2.2 | Notes |
|---|---|---|---|---|---|---|
| | | the Device | Device | | | Professional" or "Lay User/Patient." If none applicable, then specify the "Other" value |

* 21 CFR 314.80(c)(1) and 600.80(c)(1) use the term "15-day Alert reports." In the combination product PMSR final rule (21 CFR 4.101), these reports are defined as "Fifteen-day reports."

† Periodic non-expedited ICSRs are the reports required under 21 CFR 314.80(c)(2)(ii)(B) and 21 CFR 600.80(c)(2)(ii)(B) for serious, expected and nonserious adverse drug experiences.

## I. Data Elements for Electronic Submissions of IND Safety Reports

To ensure the successful processing of your electronic IND ICSR submission, you should populate the following data elements as described in Table 8.

**Table 8. Investigational New Drug Clinical Data Elements**

| Data Element | DTD Descriptor 3.0 | Title | Description | Field Length | Element Values for DTD 3.0 | Notes |
|---|---|---|---|---|---|---|
| A.1.4 | <reporttype> | Type of Report | | 1N | 1=Spontaneous<br>2=Report from Study<br>3=Other<br>4=Not Available to Sender (unknown) | Element value= 2 for Report from Study |
| A.1.9 | <fulfillexpeditecriteria> | Does this case fulfill the local criteria for an expedited report? | | 1N | 1=Yes<br>2=No<br>4=5-Day<br>5=30-Day<br>6=7-Day | Element value=1 for 15-Day Expedited<br><br>Element value= 6 for 7-Day Expedited |
| A.1.12 | <linkreportnumb> | Identification Number of the report which is linked to this report | | 100AN | | Used to link all individual cases (safetyreportid) that make up an IND Safety Report submitted as a result of an Aggregate Analysis as per 312.32(c)(1)(i)(C) or for several events |

| Data Element | DTD Descriptor 3.0 | Title | Description | Field Length | Element Values for DTD 3.0 | Notes |
|---|---|---|---|---|---|---|
| | | | | | | submitted as per (312.32(c)(1)(i)(B)) when a Narrative Summary Report is provided, this field should be populated in the IND Safety Report that contains the Narrative Summary Report. |
| A.2.3.1 | <studyname> | Study Name | | 100AN | Study ID_$Abbreviated Trial Name | The Study ID should be the same value used in the study tagging file format of the eCTD submission. |
| A.2.3.2 | <sponsorstudynumb> | Sponsor Study Number | | 35AN | IND number under which the clinical trial where the event occurred is conducted<br><br>Use the "Parent" IND number* for reports submitted from an Aggregate Analysis as per (312.32(c)(1)(i)(C)) or for several events | Populate this field with the Primary IND in the first block and repeat block A.2 with elements A.2.3.2 and A.2.3.3.as noted below with element value= 5 for sponsor's other INDs evaluating suspect product (where applicable)<br>Include the acronym "IND" followed by a space and then the IND |

| Data Element | DTD Descriptor 3.0 | Title | Description | Field Length | Element Values for DTD 3.0 | Notes |
|---|---|---|---|---|---|---|
| | | | | | submitted as per (312.32(c)(1)(i)(B)), from trials conducted under more than one IND | number for the application (e.g. IND 123456)<br>See Appendix II (Case Scenarios) for additional information on how to submit reports from sponsor's other INDs (Cross-reporting). |
| A.2.3.3 | <observestudytype> | Study type in which the Reaction(s)/ Event(s) were observed | | 1N | 1= Clinical Trials<br><br>2= Individual Patient Use (e.g., 'Compassionate Use' or 'Named Patient Basis')<br><br>3= Other Studies (e.g., Pharmacoepidemiology, Pharmacoeconomics, Intensive Monitoring)<br><br>4= Report from | Required if element value for A.1.4 is 2=Report from Study<br><br>Repeat this field as needed with element value= 5 for each Cross-reported IND.<br><br>The first block of this element in the report must not be 5.<br><br>If element value 4 is chosen, then A.1.9= 1.<br><br>See Appendix II (Case |

| Data Element | DTD Descriptor 3.0 | Title | Description | Field Length | Element Values for DTD 3.0 | Notes |
|---|---|---|---|---|---|---|
| | | | | | Aggregate Analysis as per 312.32(c)(1)(i)(C) or for several events submitted as per 312.32(c)(1)(i)(B) if a Narrative Summary Report is provided<br><br>5= Cross-reported IND Safety Report | Scenarios) for additional information on how to submit reports from an Aggregate Analysis. |
| B.1.1 | <patientinitial> | Patient Identifier | | 10AN | | For a report from an Aggregate Analysis as per 312.32(c)(1)(i)(C) or for several events submitted as per 312.32(c)(1)(i)(B) if a Narrative Summary Report is provided, the element value should be "AGGREGATE" |
| B.4.k.2.1 | <medicinalproduct> | Proprietary Medicinal Product Name | | 70AN | | For investigational drug and biological products without an established name (i.e. INN or USAN |

| Data Element | DTD Descriptor 3.0 | Title | Description | Field Length | Element Values for DTD 3.0 | Notes |
|---|---|---|---|---|---|---|
| | | | | | | name), prior to submitting IND safety reports to FAERS, the sponsor should submit a clinical information amendment to the IND, listing the names of the active drug substance/s and the medicinal product as they will be reported in E2B file submissions. The names should fit within the established E2B character length limits. Use company product code if no established name, for multi-ingredient products, or if name exceeds character length |
| B.4.k.2.2 | <activesubstancename> | Active Drug Substance Names | | 100AN | | |
| B.4.k.18 | <drugreactionrelatedness> | Relatedness of Drug to | | | | For IND Safety Reports, at least one suspect |

| Data Element | DTD Descriptor 3.0 | Title | Description | Field Length | Element Values for DTD 3.0 | Notes |
|---|---|---|---|---|---|---|
| | | Reaction/ Event | | | | product should have relatedness of drug to reaction/ event |
| B.4.k.18.1a | <drugreactionassesmeddra version> | MedDRA Version for Reaction Assessed | | 8AN | | |
| B.4.k.18.1b | <drugreactionasses> | Reaction Assessed | | 250AN | | |
| B.4.k.18.2 | <drugassessmentsource> | Source of Assessment | | 60AN | | Use the value “Sponsor” or “Investigator”. Include sponsor and investigator assessment when reporting both in separate blocks |
| B.4.k.18.3 | <drugassessmentmethod> | Method of Assessment | | 35AN | | Use the value “FDA”. |
| B.4.k.18.4 | <drugresult> | Result | | 35AN | 1=Suspected<br>2=Not suspected | For IND Safety Reports, at least one suspect product should have relatedness of drug to reaction/ event |
| B.5.1 | <narrativeincludeclinical> | Case Narrative Including Clinical | | 20,000 AN | | FDA strongly encourages sponsors to construct narratives that fit within the ICH E2B character |

| Data Element | DTD Descriptor 3.0 | Title | Description | Field Length | Element Values for DTD 3.0 | Notes |
|---|---|---|---|---|---|---|
| | | Course, Therapeutic Measures, Outcome, and Additional Relevant Information | | | | limit of 20,000 AN. If your narrative exceeds this limit, sponsors should include as much of the narrative as possible in this field and submit an ICSR attachment for any text that exceeds the character limit. Sponsors should not submit an ICSR attachment containing the entire narrative and leave the case narrative field empty.<br>For reports from Aggregate Analysis as per 312.32(c)(1)(i)(C) or for several events submitted as per 312.32(c)(1)(i)(B) where PDF is attached, put "see attached Narrative Summary Report" in this field. |

| Data Element | DTD Descriptor 3.0 | Title | Description | Field Length | Element Values for DTD 3.0 | Notes |
|---|---|---|---|---|---|---|
| B.5.4 | <sendercomment> | Sender's Comments | | 2000 AN | | Identification and analysis of previously submitted events (as required by 312.32(c)(1)) should be reported in this field. |

* The "parent IND" is the IND under which clinical investigations were initiated in the United States. (If the drug is being evaluated in multiple INDs, this is generally the IND with the lowest number.) NOTE: This may not be the same as the first A.2.3.2 block if the drug is being evaluated under multiple INDs.

NOTE: See FAERS Webpage for case scenario examples for reporting IND safety reports (e.g., IND safety reports where the sponsor is evaluating suspect product under more than one IND, IND safety reports that are a result of an aggregate analysis, and IND safety reports with unapproved and approved drugs listed as suspect products).

### J. Data Elements for Electronic Submissions of ICSRs from IND-Exempt Bioavailability (BA)/ Bioequivalence (BE) Studies

For successful processing of your electronic ICSRs submissions for a BA/BE study not conducted under an IND, you should populate the following data elements as described in Table 9.

**Table 9. Data Elements for IND-Exempt BA/BE Studies**

| Data Element | DTD Descriptor 3.0 | Title | Description | Field Length | Element Values for DTD 3.0 | Notes |
|---|---|---|---|---|---|---|
| A.1.4 | <reporttype> | Type of Report | | 1N | 1=Spontaneous<br>2=Report from Study<br>3=Other<br>4=Not Available to Sender (unknown) | Element value= 2 for Report from Study |

| Data Element | DTD Descriptor 3.0 | Title | Description | Field Length | Element Values for DTD 3.0 | Notes |
|---|---|---|---|---|---|---|
| A.1.9 | <fulfillexpeditecriteria> | Does this Case Fulfill the Local Criteria for an Expedited Report? | | 1N | 1=Yes<br>2=No<br>4=5-Day<br>5=30-Day<br>6=7-Day | Element value=1 for 15-Day Expedited<br>Or<br>Element value= 6 for 7-Day Expedited |
| A.2.3.1 | <studyname> | Study Name | | 100AN | Abbreviated Trial Name | |
| A.2.3.2 | <sponsorstudynumb> | Sponsor Study Number | | 35AN | Pre-ANDA number for the IND-Exempt BA/BE Studies | Include the acronym "Pre-ANDA" followed by a space and then the Pre-ANDA number for the application (e.g. Pre-ANDA 123456) |
| A.2.3.3 | <observestudytype> | Study Type in Which the Reaction(s)/ Event(s) were Observed | | 1N | 1= Clinical Trials<br><br>2= Individual Patient Use (*e.g., 'Compassionate Use' or 'Named Patient Basis'*)<br><br>3= Other Studies (*e.g., Pharmacoepidemiology, Pharmacoeconomics, Intensive Monitoring*)<br><br>4= Report from Aggregate Analysis as per 312.32(c)(1)(i)(C) or for | Element value="1" for Clinical Trials. |

| Data Element | DTD Descriptor 3.0 | Title | Description | Field Length | Element Values for DTD 3.0 | Notes |
|---|---|---|---|---|---|---|
| | | | | | Several Events Submitted as per 312.32(c)(1)(i)(B) if a Narrative Summary Report is Provided<br><br>5= Cross-Reported IND Safety Report | |
| B.4.k.2.1 | <medicinalproduct> | Proprietary Medicinal Product Name | | 70AN | | |
| B.4.k.1 | <drugcharacterization> | Characterization of drug role | | 1N | 1 = Suspect<br>2 = Concomitant<br>3 = Interacting<br>4 = Drug not administered | For no exposure to a study drug use 4=Drug not administered |
| B.4.k.2.2 | <activesubstancename> | Active Drug Substance Name | | 100AN | | |
| B.4.k.19 | <drugadditional> | Additional Information on Drug | | 100AN | 1 = Test drug<br>2 = Reference drug<br>3 = Placebo/Vehicle<br>4 = Control (negative or positive)<br>5 = Other drug | Specify whether the product exposed is the Test drug, Reference drug, Placebo, Vehicle, Control or Other drug |

# VI. ELECTRONIC FORMAT FOR ICSR ATTACHMENTS

FDA can accept and archive ICSR attachments in PDF format. Currently approved formats for the non-structured component of an ICSR, such as ICSR attachments, are PDF versions 1.4 (current ICH standard) or 1.6 (current version in use at FDA). An ICSR attachment should be electronically submitted to FAERS after the associated ICSR has been submitted and accepted by FAERS.

## A. Converting the ICSR Attachment to PDF

Applicants should provide an individual PDF file for each ICSR attachment. If you are submitting multiple ICSR attachments for a particular ICSR, include each attachment in the same PDF file and provide a PDF bookmark to distinguish each attachment. For example, if you are submitting a hospital discharge summary and an autopsy report for a single ICSR, include both in a single PDF file with a bookmark to the hospital discharge summary and a bookmark to the autopsy report.

## B. Identification Information in the PDF Document Information Fields

Each PDF file contains fields to be completed by the author of the document. FAERS uses these fields to locate and retrieve the attachments to specific ICSRs. To enable FDA to match the attachment(s) to the correct ICSR, applicants should fill in the PDF document information fields with the appropriate E2B(R2) data elements for the ICSR as indicated in Table 10.

**Table 10. Document Information Fields in ICSR Attachments**

| PDF Document Information Field | Include/ Optional | Document Information* | Length |
|---|---|---|---|
| Title | Include | A.1.0.1 <safetyreportid> Sender's (Case) Safety Report Unique Identifier | 100AN |
| Subject | Include | A.1.10.1 <authoritynumb> Regulatory Authority's Case Report Number OR A.1.10.2 <companynumb> Other Sender's Case Report Number | 100AN |
| Author | Optional | A.1.11.2 <duplicatenumb> Other Identification Number | 100AN |
| Keywords | Optional | A.1.7b <receiptdate> Date of Receipt of the Most Recent Information for this ICSR | 8N |

* The information refers to the data elements in E2B(R2)

In addition:

- Use the ISO-8859-1 character set for the information fields.
- Do not exceed the character length indicated above for each information field.
- Avoid creating any custom fields with names identical to the information fields listed in Table 10.

If you need assistance, you can contact the FAERS electronic submission coordinator at faersesub@fda.hhs.gov.

## VII. SUBMISSION RULES

The submission rules define the condition that shall result in a negative acknowledgement and not be accepted by FAERS.

**Table 111. Submission Rules and Acknowledgement Status**

| Data Element | DTD Descriptor 2.1/2.2/3.0 | Rejection Rule Description | Acknowledgement |
|---|---|---|---|
| NA | NA | ICSR submitted via AS2 Header where XML file: AERS<br>or<br>Routing ID where XML file: FDA_AERS and using DTD 3.0 | reportacknowledgmentcode (B.1.8) = 02 |
| NA | NA | ICSR submitted via AS2 Header where XML file: AERS_PREMKT<br>or<br>Routing ID where XML file: FDA_AERS_PREMKT and using DTD 2.1 or 2.2 | reportacknowledgmentcode (B.1.8) = 02 |
| A.1.FDA.16 | <fdasafetyreporttype> | ICSR submitted via AS2 Header where XML file: AERS_PREMKT<br>or<br>Routing ID where XML file: FDA_AERS_PREMKT using DTD 3.0 and data value is empty | reportacknowledgmentcode (B.1.8) = 02 |
| A.2.3.2 | <sponsorstudynumb> | ICSR submitted via AS2 Header where XML file: AERS_PREMKT<br>or<br>Routing ID where XML file: FDA_AERS_PREMKT using DTD 3.0 and data value is empty or not prefixed with 'IND' or 'Pre-ANDA' | reportacknowledgmentcode (B.1.8) = 02 |

## APPENDIX I. EXAMPLES OF CORRECT AND INCORRECT APPLICATION NUMBER AND DRUG ELEMENT FORMATS

**Table 122. Examples of Application Number Formats and Drug Element Formats**

| Examples of Application Number Format | | Comment |
|---|---|---|
| Correct | <drugauthorizationnumb>NDA 012345</drugauthorizationnumb> | |
| Correct | <drugauthorizationnumb>BLA 123456</drugauthorizationnumb> | |
| Correct | <drugauthorizationnumb>NDA 012345</drugauthorizationnumb><br><drugauthorizationholder>COMPANYX</drugauthorizationholder> | |
| Incorrect | <drugauthorizationnumb>123456**/10300**</drugauthorizationnumb> | Use the appropriate prefix for the NDA/ ANDA/ STN/ BLA/ PLA. Do not include additional data after the application number |
| Incorrect | <drugauthorizationnumb>NDA **12-345;IND12,345** </drugauthorizationnumb> | Omit hyphens and commas in the application number. Do not populate the tag with two application numbers |
| Incorrect | <drugauthorizationnumb>**OTC Product**</drugauthorizationnumb> | For a non-prescription drug product marketed without an approved application (Non-Rx No Application), use “999999" |
| Incorrect | <drugauthorizationnumb>NDA 012345**(COMPANYX)**</drugauthorizationnumb><br><drugauthorizationholder></</drugauthorizationholder> | Do not populate the company name in the <drugauthorizationnumb> tag |

| Examples of Application Number Format | | Comment |
|---|---|---|
| Correct | <medicinalproduct>TYLENOL</medicinalproduct><br><activesubstancename>ACETAMINOPHEN</activesubstancename> | |
| Correct | <medicinalproduct>MIRACLE WONDER DRUG</medicinalproduct><br><activesubstancename>ACETAMINOPHEN</activesubstancename> | |
| Incorrect | <medicinalproduct>AMAZING DRUG **OTC®**</medicinalproduct><br><activesubstancename>ACETAMINOPHEN **500 mg**</activesubstancename> | |
| Incorrect | <medicinalproduct>NEW DRUG **40 mcg/mL**</medicinalproduct><br><activesubstancename>NEWSUBSTANCE **Inj** </activesubstancename> | |
| Incorrect | <medicinalproduct>**MWD**</medicinalproduct><br><activesubstancename>**APAP**</activesubstancename> | Do not use abbreviations for the brand name or active substance in the <medicinalproduct> and <activesubstance> tags |

## APPENDIX II. CASE SCENARIOS FOR IND SAFETY REPORTS SUBMITTED TO FAERS

The following case scenarios are intended to provide examples to sponsors on the use of ICH E2B data standard elements for submission of IND safety reports to FAERS that may differ from postmarketing safety reports.

1. For any IND safety report where the sponsor is evaluating the suspect product under more than one IND (i.e. "Cross-reporting")
    a. Repeat block A.2 for each IND
        i. Use first block A.2 to designate IND where the event occurred = "primary IND"
            1. A.2.3.2 = primary IND
            2. A.2.3.3 = data value could either be 1, 2, 3, or 4
            3. Other relevant information for the report to be populated in block A.2
        ii. Repeat block A.2 as many times as needed with only the following data elements for each IND that the sponsor holds where that suspect product is being evaluated:
            1. A.2.3.2 = IND number for each cross-reported IND

            and

            2. A.2.3.3 = 5

**Table 133. Case Scenario 1. For IND Safety Reports Submitted to FAERS**

| Data Element | DTD Descriptor 3.0 | Title | Element Values for DTD |
|---|---|---|---|
| A.2.3.2 | <sponsorstudynumb> | Sponsor Study Number | IND number under which the Clinical Trial where the event occurred is conducted |

| Data Element | DTD Descriptor 3.0 | Title | Element Values for DTD |
|---|---|---|---|
| A.2.3.3 | <observestudytype> | Study Type in Which the Reaction(s) were observed | 1= Clinical Trial<br><br>2= Individual Patient Use (*e.g. 'Compassionate Use' or 'Named Patient Basis'*)<br><br>3= Other Studies (*e.g. Pharmacoepidemiology, Pharmacoeconomics, Intensive Monitoring*)<br><br>4= Report from Aggregate Analysis 312.32(c)(1)(i)(C) or for several events submitted as per 312.32(c)(1)(i)(B) if a Narrative Summary report is provided.<br><br>5=Cross-reported IND safety report |

2. For an IND safety report that is a result of an aggregate analysis as per 312.32(c)(1)(i)(C) or for several events submitted as per 312.32(c)(1)(i)(B) if a narrative summary report is provided:

    a. Submit one IND safety report with the IND where the event occurred in A.2.3.2 <sponsorstudynumb> (or the "parent" IND if the events occurred in multiple INDs).

    For this IND safety report, populate the data elements below in addition to other relevant information regarding the event and suspect product.

        i. Use data element = 4 in A.2.3.3<observestudytype>

        ii. Use the term "AGGREGATE" in B.1.1 <patientinitial>

    b. Section VII.A.2. of the *FDA Guidance for Industry – "Safety Reporting Requirements for INDs and BA/BE Studies" (December 2012)* discusses several submission requirements for IND safety reports that are a result of an aggregate analysis. The following two sections describe these submission elements and how they are accomplished with electronic submission to FAERS.

        1. The guidance states that IND safety reports that are a result of an aggregate analysis should contain a narrative description of the event and the results of the analysis (hereafter referred to as a "narrative

summary report"). For IND reports submitted to FAERS, attach the narrative summary report to the IND safety report as a PDF attachment (do not put the narrative summary report in the E2B narrative field).

a. These instructions also apply to several events submitted as per 312.32(c)(1)(i)(B) if a narrative summary report is provided.

2. The guidance states that all the individual cases that were analyzed in the aggregate analysis should be submitted. Use the repeatable block A.1.12 to link all the safety report numbers for the individual supportive ICSRs (i.e. the numbers in A.1.0.1 for all the individual cases that are summarized in the narrative summary report).

a. These instructions also apply to several events submitted as per 312.32(c)(1)(i)(B) if a narrative summary report is provided.

b. IND safety reports previously submitted as ICSRs to FAERS do not have to be resubmitted (place the safety report numbers for these previously submitted reports in A.1.12).

c. For IND safety reports previously submitted in eCTD format, the sponsor should list the eCTD sequence number and date of submission in the narrative summary report. (The eCTD sequence number is the unique four-digit number for each IND submission the sponsor submits in the us-regional.xml file for the eCTD submission.)

d. IND safety reports previously submitted on paper should be attached to the IND safety report as PDF attachments.

**Table 144. Case Scenario 2. For IND Safety Reports Submitted to FAERS**

| Data Element | DTD Descriptor 3.0 | Title | Element Values for DTD |
|---|---|---|---|
| A.1.12 | <linkreportnumb> | Identification number of the report(s) which are linked to this report | Used to link all individual cases (safetyreportid) that make up an IND Safety Report submitted as a result of an Aggregate Analysis as per 312.32(c)(1)(i)(C) or for several events submitted as per 312.32(c)(1)(i)(B) if a narrative summary report is provided |
| A.2.3.2 | <sponsorstudynumb> | Sponsor Study Number | IND number under which the Clinical Trial where the event occurred is conducted |

| Data Element | DTD Descriptor 3.0 | Title | Element Values for DTD |
|---|---|---|---|
| A.2.3.3 | <observestudytype> | Study Type in Which the Reaction(s) were Observed | 1= Clinical Trials<br><br>2= Individual Patient Use (*e.g. 'Compassionate Use' or 'Named Patient Basis'*)<br><br>3= Other Studies (*e.g. Pharmacoepidemiology, Pharmacoeconomics, Intensive Monitoring*)<br><br>4= Report from Aggregate Analysis 312.32(c)(1)(i)(C)<br><br>5=Cross-reported IND safety report |
| B.1.1 | <patientinitial> | Patient Identifier | For a Report from an Aggregate Analysis, the element value should be "AGGREGATE" |

3. For adverse events that occur with a marketed drug being evaluated under an IND that meets both IND and post-marketing safety reporting requirements (21 CFR 312.32 and 314.80, 600.80, or 310.305), sponsors must submit two separate ICSRs:

    a. for the marketed drug for the NDA/BLA

    and

    b. for the study drug for the IND (IND number in A.2.3.2)

## APPENDIX III. CASE SCENARIOS FOR SAFETY REPORTS FROM IND-EXEMPT BA/BE STUDIES TO FAERS

Table 15 illustrates the ICH E2B data elements and element values for each IND-exempt BA/BE study exposure scenario described below:

Scenario 1: Exposure to a *study drug*:

This scenario applies to all drugs specified in the study protocol. For example, if a BA/BE study protocol for a generic opiate includes administration of naltrexone to each study subject prior to administration of a test or reference drug, naltrexone is a *study drug*, although it is not the test or reference drug. Similarly, a selective 5-HT3 receptor antagonist to prevent nausea and vomiting is considered a *study drug* if the BA/BE study protocol states that the drug is administered to each study subject prior to administration of a test or reference drug.

Scenario 2: Exposure to an *other drug*:

*Other drugs* are drugs taken by or administered to a subject that are not part of study conduct per protocol. For example, a subject with a diagnosis of hypertension has normal blood pressure while treated with a beta blocker. The subject meets study enrollment criteria and continues to take his beta blocker during study participation. In this situation, the beta blocker is an *other drug*. Similarly, if a subject develops symptoms of heartburn during participation in a BA/BE study and is permitted, by the investigator, to use a nonprescription antacid or H2 blocker for symptomatic relief, the nonprescription drug taken by the subject is an *other drug*.

Scenario 3: No exposure to a study drug:

A serious adverse event a subject experiences after enrollment to the study, but prior to exposure to a study drug, is subject to the expedited safety reporting requirement. To report a serious adverse event with no study drug exposure, the submitter should select values as shown in the Table 15, Scenario 3.

**Table 155. ICH E2B Data Element & Value Selections for IND-Exempt BA/BE Study Exposures**

| Drug Exposure Scenario | Data Element | Element Values |
|---|---|---|
| Scenario 1:<br>Exposure to a *study drug* | B.4.k.1 | Select one element value |
| | B.4.k.2.1 | Proprietary medicinal product name |
| | B.4.k.2.2 | Drug substance name |
| | B.4.k.19 | Select one from the following:<br>1 = Test drug<br>2 = Reference drug<br>3 = Placebo/Vehicle<br>4 = Control (negative or positive) |
| Scenario 2:<br>Exposure to an *other drug* | B.4.k.1 | Select one element value |
| | B.4.k.2.1 | Proprietary medicinal product name |
| | B.4.k.2.2 | Drug substance name |
| | B.4.k.19 | 5 = Other drug |
| Scenario 3:<br>No exposure to a *study drug* | B.4.k.1 | 4 = Drug not administered |
| | B.4.k.2.1 | Proprietary medicinal product name |
| | B.4.k.2.2 | Drug substance name |
| | B.4.k.19 | 1 = Test drug |